Dkt. 65019-DC-PCT-US/JPW/AJM/NFM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Marc Feldmann and Ravinder N. Maini	
Serial No.	:	09/921,937	Examiner: Not yet known
Filed	:	August 3, 2001	Group Art Unit: Not yet known
For	:	ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE TREATMENT OF AUTOIMMUNE DISEASE	

1185 Avenue of the Americas
New York, New York 10036
November 26, 2001

Hon. Commissioner for Patents
P.O. Box 2327
Arlington, Virginia 22202

Sir:

INFORMATION DISCLOSURE STATEMENT

Applicants submit herewith an Information Disclosure Statement under 37 C.F.R. §1.56.

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and 37 C.F.R. §1.97(a)-(b)(2), applicants would like to direct the Examiner's attention to the following publications which are listed on the attached Form PTO-1449 (**Exhibit A**). Copies of cited publications 1-5 and 12 are attached hereto as **Exhibits 1 - 6,** respectively. Publications 6-11 and 13-60 were entered in prior application U.S. Serial No. 08/690,775 (filed August 1, 1996), to which priority under 35 U.S.C. §120 is claimed. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information

Disclosure Statement.

1. U.S. Patent No. 6,015,557, issued January 18, 2000 (Tobinick et al.) (**Exhibit 1**);

2. U.S. Patent No. 6,177,077 B1, issued January 23, 2001 (Tobinick) (**Exhibit 2**);

3. U.S. Patent No. 5,795,967, issued August 18, 1998 (Aggarwal et al.) (**Exhibit 3**);

4. U.S. Patent No. 5,958,413, issued September 28, 1999 (Anagnostopulos et al.) (**Exhibit 4**);

5. U.S. Patent No. 6,190,691 B1, issued February 20, 2001 (Mak et al.) (**Exhibit 5**);

6. U.S. Patent No. 5,656,272, issued August 6, 1997 (Le et al.);

7. U.S. Patent No. 5,741,488, issued April 21, 1998 (Feldmann et al.);

8. U.S. Patent No. 5,698,195, issued December 16, 1997 (Le et al.);

9. U.S. Patent No. 5,919,452, issued July 6, 1999 (Le et al.);

10. U.S. Patent No. 5,317,019, issued May 31, 1994 (Bender et al.);

11. U.S. Patent No. 5,672,347, issued September 30, 1997 (Aggarwal et al.);

12. PCT Publication No. WO 00/50079, published August 31, 2000 (**Exhibit 6**);

13. PCT Publication No. WO 92/08474, published May 29, 1992;

14. PCT Publication No. WO 92/07585, published May 14, 1992;

15. PCT Publication No. WO 92/16553, published October 1, 1992;

16. PCT Publication No. WO 95/09652, published April 13, 1995;

17. PCT Publication No. WO 96/33204, published October 24, 1996;

18. PCT Publication No. WO 98/24463, published June 11, 1998;

19. PCT Publication No. WO 89/08460, published September 21, 1989;

20. Barrera, P., et al., "Effects of a Weekly Dosis of Methotrexate on IL-1, TNF and IL-6 in patients with Rheumatoid Arthritis," *Cytokine*, 3(5):504, Abstract 330 (1991);

21. Bologna, C., and Sany, J., "Association des Traitements de Fond dans la Polyarthrite Rhumatoide," *Presse Med.*, 25:876-878 (1996);

22. Borigini, M.J., and Paulus, H.E., "Combination Therapy,"

Bailliére's Clin. Rheum., 9(4):689-710 (1995);

23. Brahn, E. et al., "Effects of Tumor Necrosis Factor and Combination Cyclosporine A/Methotrexate Therapy on Collagen Arthritis," *Arthritis & Rheumatism*, 32 (Suppl. 4):S133 (1992), Abstract D42;

24. Breedveld, F., et al., "Anti-CD4 Antibodies in Rheumatoid Arthritis," *Clinical and Experimental Rheumatology*, 10(4):325-326 (1992);

25. Brennan, F., et al., "Inhibitory Effect of TNFα Antibodies on Synovial Cell Interleukin-1 Production in Rheumatoid Arthritis," *The Lancet*, 2(8657):244-247 (1989);

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28. Choy, E.H.S., et al., "Therapeutic Monoclonal Antibodies," *British J. Rheumatology*, 34:707-715 (1995);

29. Cohen, S., et al., "Comparison of the Safety and Efficacy of Cyclosporine-A and Methotrexate in Refractory Rheumatoid

Arthritis: A Randomized, Multi-Centered Placebo-Controlled Trial," *Rev. Esp. Rheumatol.*, 20 Suppl. 1:148 (1993), Abstract 318;

30. Debets, R., et al., "Cytokine Antagonists and their Potential Therapeutic Use," *Immunology Today*, 15:455-458 (1994);

31. Elliott, M.J. et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to TNF-α: Safety, Clinical Efficacy and Control of the Acute Phase Response," *Cell. Biochemistry, Supplement*, 0(17B):145 (1993); Abstract EZ405;

32. Elliott, M.J. et al., "Treatment of Rheumatoid Arhritis with Chimeric Monoclonal Antibodies to TNFα", *Rev. Esp. Reumatol*, 20 Suppl. 1:148 (1993); Abstract 320;

33. Elliott, M.J., et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factorα," *Arth. Rheum.*, 36(12):1681-1690 (1993);

34. Elliott, M.J., et al., "Randomised Double-Blind Comparison of Chimeric Monoclonal Antibody to Tumor Necrosis Factorα (cA2) Versus Placebo in Rheumatoid Arthritis," *The Lancet* 344:1105-1110 (1994);

35. Elliott, M.J., et al., "Repeated Therapy with Monoclonal Antibody to Tumor Necrosis Factor α (cA2) in Patients with Rheumatoid Arthritis," *The Lancet* 344:1125-1127 (1994);

36. Hervé, P., et al., "Phase I-II Trial of a Monoclonal Anti-Tumor Necrosis Factor α Antibody for the Treatment of Refractory Severe Acute Graft-Versus-Host Disease," *Blood*, 79:3362-3368 (1992);

37. Horneff, G., et al., "Elevated Levels of Circulating Tumor Necrosis Factor-α, Interferon-γ, and Interleukin-2 in Systemic Reactions Induced by Anti-CD4 Therapy in Patients with Rheumatoid Arthritis," *Cytokine*, 3(3):266-267 (1991);

38. Horneff, G., et al., "Treatment of Rheumatoid Arthritis with an Anti-CD4 Monoclonal Antibody," *Arthritis & Rheumatism*, 34(2):129-140 (1991);

39. Kalden, J.R., and Manger, B., "Biologic Agents in the Treatment of Inflammatory Rheumatic Diseases," *Curr. Opin. Rheum.* 7:191-197 (1995);

40. Kalden, J.R., and Manger, B., "Biologic Agents in the Treatment of Inflammatory Rheumatic Diseases," *Curr. Opin. Rheum.*, 9:206-212 (1997);

41. Kavanaugh, A., et al., "Anti-TNF-α Monoclonal Antibody (mAb) Treatment of Rheumatoid Arthritis (RA) Patients With Active Disease On Methotrexate (MTX); Results of a Double-Blind, Placebo Controlled Multicenter Trial," *Arth. Rheum.*, 39 (Suppl. 9):18-22 (October 1996), Abstract 575;

42. Kozarek, R.A., et al., "Methotrexate Induces Clinical and

Histologic Remission in Patients with Refractory Inflammatory Bowel Disease," *Ann. Int. Med.*, 110:353-356 (1989);

43. Maini, R.N., et al., "Clinical Response of Rheumatoid Arthritis (RA) to Anti-TNFα (cA2) Monoclonal Antibody (mab) is Related to Administered Dose and Persistence of Circulating Antibody," *Arth. Rheum. Supplement*, 38(9):S186 (1995); Abstract 200;

44. Maini, R.N., "The Role of Cytokines in Rheumatoid Arthrits," *J. Royal College of Physicians of London*, 30(4):344-351 (1996);

45. Manual of Medical Therapeutics, 25th Edition, Orian et al., (editors), Dept. of Medicine, Washington University, St. Louis, MO, Pages 308-309 (1986);

46. Markowitz, J., et al., "Immunology of Inflammatory Bowel Disease: Summary of the Proceedings of the Subcommittee on Immunosuppresive Use in IBD," *Journal of Pediatric Gastroenterology and Nutrition*, 12(4):411-423 (1991);

47. Natanson, C. et al., "Selected Treatment Strategies for Septic Shock Based on Proposed Mechanisms of Pathogenesis," *Ann. Int. Med.*, 120(9):771-783 (1994);

48. Pascalis, L., et al., "Longterm Efficacy and Toxicity of Combined Cyclosporine A-Steroid-Methotrexate Treatment in Rheumatoid Arthritis," *Rev. Esp. Rheumatol.*, 20 Suppl. 1:148

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49. Paul, W.E., ed., *Fundamental Immunology*, 3rd edition (NY: Raven Press) page 242 (1993);

50. Paul, W.E., ed., "Tumor Necrosis Factor," In *Fundamental Immunology*, 3rd edition (NY:Raven Press), pages 807-812 (1993);

51. Racadot, E., "Immunological Follow-up of 17 Patients with Rheumatoid Arthritis Treated *in vivo* with an Anti-T CD4+ Monoclonal Antibody (B-F5)," *Clinical and Experimental Rheumatology*, 10:365-374 (1992);

52. Ralph, P., "Clinical and Preclinical Studies Presented at the Keystone Symposium on Arthritis, Related Diseases, and Cytokines," *Lymphokine and Cytokine Research.*, 12(4):261-263 (1993);

53. Rankin, E.C.C., et al., "The Therapeutic Effects of an Engineered Human Anti-Tumour Necrosis Factor Alpha Antibody (CDP571) in Rheumatoid Arthritis," *British J. Rheumatology*, 34: 334-342 (1995);

54. Schact, E., "Gegenwärtige und Zukünftige Therapiestrategien der Rheumatoiden Arthritis (RA)," ["The Current and Future Therapy Strategies of Rheumatoid Arthritis (RA)"], *Zeitschrift für Rheumatologie*, 52(6):365-382 (1993);

55. Steinbruchel, D., et al., "Monoclonal Antibody Treatment

(anti-CD4 and anti-interleukin-2 receptor) Combined with Cyclosporin A has a Positive but not Simple Dose-Dependent Effect on Rat Renal Allograft Survival," *Scandinavian J. Immunol.*, 34(5):627-633 (1991);

56. Van Der Lubbe, P.A., et al., "A Randomized, Double-Blind, Placebo-Controlled Study of CD4 Monoclonal Antibody Therapy in Early Rheumatoid Arthritis," *Arth. Rheum.*, 38(8):1097-1106 (1995);

57. Van Dullemen, H.M., et al., "Treatment of Crohn's Disease with Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)," *Gastroenterlogy*, 109(1):129-135 (1995);

58. Watts, R.A., and Isaacs, J.D., "Immunotherapy of Rheumatoid Arthritis," *Annals Rheumatic Diseases*, 51:577-579 (1992);

59. Williams, R.O., et al., "Successful Therapy of Collagen-Induced Arthritis with TNF Receptor-IgG Fusion Protein and Combination with Anti-CD4," *Immunology*, 84:433-439 (March 1995); and

60. Williams, R.O., et al., "Synergy Between Anti-CD4 and Anti-Tumor Necrosis Factor in the Amelioration of Established Collagen-Induced Arthritis," *Proc. Natl. Acad. Sci. USA*, 91:2762-2766 (1994).

Each of the above-listed publications is listed again on the accompanying PTO Form 1449 (**Exhibit A**).

Applicants request that the Examiner review the publications and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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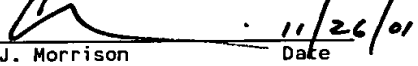

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Alan J. Morrison Date
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INFORMATION DISCLOSURE CITATION
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Atty. Docket No. 65019-DC-PCT-US/JPW/AJM/NFM	Serial No. 09/921,937
Applicants Marc Feldmann et al.	
Filing Date August 3, 2001	Group Not yet known

U.S. PATENT DOCUMENTS

Examiner Initial			Date	Name	Class	Subclass	Filing Date if Appropriate
		6,015,557	01/18/00	Tobinick et al.			
		6,190,691	02/20/01	Mak			
		6,177,077	01/23/01	Tobinick			
		5,795,967	08/18/98	Aggarwal et al.			
		5,958,413	09/28/99	Anagnostopulos et al.			
		5,656,272	08/12/97	Le et al.			
		5,741,486	04/21/98	Feldmann et al.			
		5,698,195	12/16/97	Le et al.			
		5,919,452	07/06/99	Le et al.			
		5,310,646	05/31/94	Bender et al.			
		5,672,347	09/30/97	Aggarwal et al.			

FOREIGN PATENT DOCUMENTS

			Date	Country	Class	Subclass	Translation Yes	Translation No
	WO	00/50075	08/31/00	PCT				
	WO	89/08460	09/21/89	PCT				
	WO	92/08460	05/29/92	PCT				
	WO	92/07581	05/14/92	PCT				
	WO	92/16553	10/01/92	PCT				
	WO	95/09654	04/13/95	PCT				
	WO	96/33273	10/24/96	PCT				
	WO	98/24463	06/11/98	PCT				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Barrera, P., et al., "Effects of a Weekly Dosis of Methotrexate on IL-1 TNF and IL-6 in patients with Rheumatoid Arthritis," *Cytokine*, 3 (5) :504, Abstract 330 (1991).
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EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. 65019-DC-PCT-US/JPW/AJM/NFM	SERIAL NO. 09/921,937
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OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

Brahn, E. et al., "Effects of Tumor Necrosis Factor and Combination Cyclosporine A/Methotrexate Therapy on Collagen Arthritis," *Arthritis & Rheumatism*, 32 (Suppl. 4) :S133 (1992), Abstract D42.

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Debets, R., et al., "Cytokine Antagonists and their Potential Therapeutic Use," *Immunology Today*, 15: 455-458 (1994).

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		Maini, R.N., et al., "Clinical Response of Rheumatoid Arthritis (RA) to Anti-TNF α (cA2) Monoclonal Antibody (mab) is Related to Administered Dose and Persistence of Circulating Antibody," *Arth. Rheum. Supplement*, 38 (9) :S186 (1995); Abstract 200.
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		Paul, W.E., ed., "Tumor Necrosis Factor," *In Fundamental Immunology*, 3rd edition (NY:Raven Press), pages 807-812 (1993).
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		Van Dullemen, H.M., et al., "Treatment of Crohn's Disease with Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)," *Gastroenterlogy*, 109 (1) :129-135 (1995).
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